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Unmet needs in Parkinson's disease: New horizons in a changing landscape

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ABSTRACT

The success of levodopa and other classes of drugs have meant that most people with Parkinson's disease enjoy a good quality of life for many years. However, despite the availability of several drugs and formulations that can be used as monotherapy and in combination, there are a number of disease features that the current therapies are unable to address. The disease continues to progress despite treatment, patients suffer from a myriad of motor and non-motor symptoms, and a neuroprotective therapy is urgently required. To move forward with medical and surgical management, it is important to consider new insights that recent research offers and in this review we examine how a better understanding of the disease pathology and progression might improve and enrich our daily clinical practice. It is also timely to consider the service provision changes that will increasingly be needed to effectively manage the needs of the aging population.

1. Introduction

Parkinson's disease (PD) is among the most common neurodegenerative disorders, the prevalence of which increases with advancing age. With today's rapidly ageing society it is predicted that the PD patient population will at least double by 2030 [1], and the associated increase in medical costs will be considerable [2]. The success of levodopa and other drug classes has meant that most patients can enjoy a good quality of life for many years [3,4]. However, despite the availability of several drugs and formulations that can be used as monotherapy and in combination, there are a number of disease features that the current therapies are unable to address.

Key medical unmet needs in PD include the need for better animal models replicating the parkinsonian process, slowing of disease progression/neuroprotection, improved biomarkers (imaging, genetic, clinical or other modality), improved 24-h control of motor fluctuations in moderate to advanced disease and more effective treatment of non-motor symptoms (NMS). Nocturnal symptoms as well as early morning fluctuations (motor and NMS) remain neglected [5]. To move forward with medical management, it is important to consider new insights that recent research offers and in this review we examine how a better understanding of the disease pathology and progression might inform our daily clinical practice.

2. Research challenge

2.1. Animal models of disease pathology

As past research focused on dopaminergic replacement therapy for motor symptoms, the traditional dopamine lesion models (i.e. the 6-hydroxydopamine rat model and MPTP-treated monkey models) formed an important basis for drug development. Indeed, these models were generally helpful in predicting symptomatic motor responses to dopaminergic therapy [6]. However, these have been of limited value in predicting the results of potential neuroprotective therapies, and this is fundamentally because they do not reflect the true complex etiopathogenesis of PD, neither do they

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show progression or Lewy body formation [7]. Additional preclinical models have been developed and these are summarized in Table 1. However, no current preclinical model is able to adequately mirror the tremendous complexity of PD itself.

Indeed, there have been significant advances in understanding the pathophysiology of PD over the past decades and it is now better understood that the disease follows a defined clinical pattern, with a range of NMS defining the pre-motor phase [8]. In the prodromal stage, the most common NMS manifestations are olfactory impairment and raid eye movement behavior disorder while other features such as constipation, somnolence, apathy, fatigue may also be present [9]. The development of many of these symptoms is consistent with the Braak pathology staging in which Lewy bodies first develop in the dorsal motor nucleus of the vagus nerve, the olfactory bulb, enteric nervous system and the submandibular gland, and then later spread to the substantia nigra, areas of the midbrain and basal forebrain, and finally reach areas of the neocortex [10]. Indeed, recent research has implicated the vagus nerve and the gut-brain axis as a potential generator of the pathological process in PD [11]. Added to this complexity, many cellular mechanisms such as protein degradation, oxidative stress, mitochondrial defects, proteolytic stress, neuroinflammation, an impaired ubiquitin protesomal system and autophagy have been suggested to play a role in PD [12]. None of the currently used models of disease, and certainly none of the toxin-induced lesion models, reliably reflect this complex neuropathology – representing a key unmet scientific need in PD [13].

2.2. Biomarkers of disease progression

New MDS diagnostic criteria for PD have moved away from an approach wholly based on motor symptoms to a combination of central core motor and non-motor features [14]. In this respect, clinical, genetic and imaging biomarkers are emerging as strong predictors of diagnosis and progression – although much work still needs to be done to exactly define the specificity and sensitivity of such tests [15]. The availability of a biomarker battery or package would enable accurate and early diagnosis based on objective evidence allowing for improved individualized therapy as well as for monitoring progression. Indeed, a good biomarker or biomarkers could be used to confirm diagnosis, assess disease progression, and even identify individuals who are in the prodromal stages of the disease [16–18].

Biomarkers can be categorized as '*trait*' (biomarkers which are stable over time), '*state*' (biomarkers which change with disease progression or treatment), and '*pharmacodynamic*' (sometimes referred to as mechanism of action markers). Several potential biomarkers have been pursued, ranging from neuroimaging to possible markers in the blood [19], CSF [20], and even the colon [21]. Specifically, molecular pathways related to α-synuclein, tau and β-amyloid peptides have received considerable attention. Such advances have been extensively reviewed elsewhere [22–25]. Although there are several promising candidates under evaluation, there is increasing consensus that no single candidate will provide full utility in isolation. A combinatorial approach, using a variety of approaches that take into account the multifactorial pathogenesis of PD will likely be necessary. Recent evidence also suggests that sleep and imaging measures, and to some extent NMS (assessed using appropriate NMS scales) may be more helpful than currently available CSF biomarkers and cognitive scales in quantifying progression [15].

2.3. Understanding PD phenotype and disease progression

It is well established that rates of disease progression in PD can be variable, and the motor subtype divisions of 'tremor dominant' versus 'postural instability/gait difficulty' (PIGD) parkinsonism have been broadly accepted and used in a variety of clinical studies [26–29]. Although definitions and methodologies have varied, studies generally have reported a worse prognosis in terms of disability, quality of life, disease progression and risk of dementia for patients with the PIGD phenotype as compared with the tremor dominant phenotype [30–33]. However, accumulating evidence is bringing the longitudinal stability of these phenotypes into question [34]. The Parkinson's Progression Markers Initiative (PPMI) has published one-year analysis data from patients who were untreated at the time of enrollment. The study found substantial instability of motor subtype; almost a third (29%) of patients originally classified as having PIGD dominant disease shifted to a tremor dominant phenotype during the first year of diagnosed disease [35]. This instability of motor phenotypes, and the recognition that PD subtypes are largely characterized by the severity of non-dopaminergic features has led to evaluation of non-motor symptoms as an alternative scheme.

According to the concept of NMS subtyping, the predominant NMS symptoms experienced will depend on which non-dopaminergic nuclei (in the limbic and brainstem areas) are most affected by the underlying disease neuropathology and spread. In one recent proposal, Sauerbier et al. suggested at least seven distinct NMS dominant subtypes of PD: Cognitive dominant, apathy dominant, depression/anxiety dominant, sleep dominant, pain dominant, fatigue dominant and autonomic dominant [8]. Within this scheme, sleep-dominant and autonomic-dominant subtypes are grouped into a 'brainstem phenotype,' where the underlying pathology is thought to involve the brainstem and olfactory route. Likewise, the cognitive dominant subtype is thought to reflect late-onset disease where cortical pathology predominates and the depression, fatigue and pain dominant subtypes are grouped under a 'limbic phenotype' where the olfactory route predominates [8]. The stability of non-motor subtypes has not been studied and it is probable that non-motor subtypes will also change throughout the disease course. Nevertheless, this form of NMS PD subtyping allows for future PD research to be more focused, by utilizing a subset of specific patients and working to improve their quality of life.

3. Treatment challenges

3.1. Neuroprotection

The prime unmet clinical need in PD is a 'neuroprotective' and/or 'disease-modifying' treatment that can halt or at least slow the progression of this progressive disease. While there have been many promising candidate agents in preclinical studies, no drug or treatment strategy has proven to be neuroprotective or disease-modifying in PD. Some of the key barriers to development of such an agent have already been described above. The lack of a robust model (or models) of disease with a prolonged prodromal period, severely impairs our ability to screen and test new products. Without validated biomarkers of disease, it is virtually impossible to prove an effect on the underlying disease progression. Recent experience with the rasagiline ADAGIO trial [36] showed us that it can be very hard to interpret clinical data, no matter how sophisticated the trial design is [37,38], and the availability of a biomarker is now considered a pre-requisite for the development of new disease-modifying treatment strategies for PD [39,40]. Moreover, since patients already have undergone significant neurodegeneration before they develop overt motor symptoms, treatment at diagnosis may already be too late for a neuroprotective agent. The only way would be to accurately identify pre-motor patients, and this would require a reliable biomarker [41].

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Table 1
Examples of current preclinical models for Parkinson's disease.

- Pharmacologic models
  - Reserpine treated rodents
  - Haloperidol treated rodents
- Neurotoxin and dopamine depletion based
  - MPTP lesioned monkeys
  - MPTP treated mice
  - 6-OHDA lesioned rats (full and partial lesions)
- Pesticide-induced models
  - Rotenone rodent model
  - Paraquat and Maneb models
- Proteasomal inhibitor models
- Glial activation models
- Synuclein deposition based
  - Transgenics
  - Viral vectors
  - Prion like propagation based
- Genetic model system based
  - PINK1
  - Parkin
  - DJ1
  - LRRK2
- Induced pluripotent cells
- Minipig models

Moreover, it is only possible to demonstrate that drug slows the rate of progression, when one has an understanding of the benchmark rate. Finally, given the heterogeneity of disease, it is entirely likely that not all medications will be suitable for all patients and an understanding of disease types will be essential.

3.2. Management of motor complications

In the absence of a neuroprotective agent, we must rely on the effective management of symptoms (motor and non-motor). At present, levodopa remains unchallenged as the most efficacious and best tolerated antiparkinsonian drug, albeit one that is often limited by the development of response fluctuations and dyskinesia [42,43]. Motor fluctuations are almost invariably associated with often disabling non motor fluctuations [44]. Patient surveys consistently highlight the negative impact that being 'OFF' has on the patient [45,46], and other studies show the significant impact of motor fluctuations on patient quality of life [3,47]. In particular, the early morning OFF state is associated with significant and distressing NMS as shown in a recent multicenter survey [48] and management of this common problem remains a key unmet need. Recent studies using apomorphine injections for first dose of the day or for dose failures in PD are therefore timely [49].

We now better understand that the dose and pulsatile pharmacokinetics of levodopa are closely associated with the development of motor complications [50–52] and, together with the development of a broad armamentarium of adjunctive therapies (i.e. dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine), we are now better equipped to design better treatment strategies for our patients with motor fluctuations. However, it is also clear that, despite all these advances, current standards of therapy do not completely abolish motor fluctuations. This is one area where a greater understanding of the full impact of disease – beyond the central nervous system – may help. For example, widespread involvement of the GI system is common in PD, with alpha synuclein and Lewy bodies demonstrated throughout the enteric nervous system, including within myenteric neurons [53] (Table 2). Indeed, it is now estimated that >70% PD patients have GI disorders, including gastric dysmotility (gastroparesis) and bacterial overgrowth [54]. Very importantly, these GI problems can occur early on in the course of PD, and should no longer be considered a feature of advanced disease [54,55]. Since levodopa and many other orally administered PD drugs are absorbed in small intestine, it is thought that these problems might be a key contributor to motor fluctuations in some patients [54]. If the drug is not absorbed, it cannot be expected to exert its therapeutic action.

The relevance of drug absorption cannot be underestimated, and has led to a reappraisal of how we view OFF episodes. Whereas, we once very much focused on 'end-of-dose wearing-off', we now increasingly consider the time taken to ON, which is related to drug absorption and has been reported to be more than twice the duration of wearing-off [56]. Nocturnal hypokinesia and early morning off is often the longest OFF period in the daily treatment cycle [5,57], and delays to ON time and dose failures have been reported to account for >60% of daily OFF time [58]. As such, this provides a rationale for using non-oral therapies such as apomorphine injections or infusion which do not rely on GI absorption to manage motor fluctuations in patients where oral treatments do not provide sufficient control. Significant advances in continuous non-oral levodopa delivery are also being made at an ever increasing rate [59].

3.3. Management of non-motor complications

As discussed above, NMS are now considered a key component of PD that are explained by the widespread pathology of the disease, and which may represent a clinical biomarker of its premotor phase [60]. The burden of non-motor symptoms can define a patient's health-related quality of life [61], and is a major contributor to increased healthcare costs [62]. However, clinicians often regard the management of NMS as being secondary to motor symptom control. This may, in part, be because clinicians do not feel as able to deal with NMS as they do with motor symptoms. Although some evidence supports the efficacy of certain treatments for depression, dementia, psychosis, constipation, orthostatic hypotension and sialorrhea, there is insufficient evidence for efficacious treatments for other important non-motor symptoms that certainly contribute to poor quality of life, such as neurogenic bladder disturbance, erectile dysfunction, fatigue, insomnia, apathy, anxiety and excessive daytime sleepiness [60,63]. The emergence of recent controlled trials concentrated on key non-motor issues such as Parkinson associated pain [64] or sleep [65] is highly encouraging. Nevertheless, the broad spectrum of NMS in PD clearly highlight the need for developing non-dopaminergic therapies that target the non-dopaminergic degeneration in PD.

It is also important to note that some NMS are dopa responsive. Levodopa response fluctuations are not limited to motor symptoms, and most patients with motor fluctuations also experience NMS fluctuations (NMS which worsen in OFF episodes) [66]. Recently, the EuroInf study clearly demonstrated that improvements in dopaminergic responsive NMS (with levodopa and apomorphine infusion) lead to robust improvements in quality of life [67].

Table 2
GI abnormalities prevalent in PD which may hamper oral drug absorption.

- Dysphagia
- Drooling
- Gastritis/H Pyori related
- Peptic ulcer/H Pylori
- Delayed Gastric emptying
- Small intestinal bacterial overgrowth (SIBO)
- Intestinal microbiota alteration

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3.4. Multidisciplinary service provision

To manage the complex needs of people with PD, it is increasingly accepted that a multidisciplinary team (MDT) approach should be developed to provide professional care in all motor and non-motor aspects of PD throughout the course of the disease. Healthcare providers are tasked not only to care for the patients but also to offer assistance to their caregivers who play a vital role along the illness trajectory. The MDT approach uses experts in PD from different health care professions as needed. Members can include a neurologist, a specialist Parkinson's nurse, a speech and language therapist, a physiotherapist, a social worker, a psychiatrist, an occupational therapist, a sexologist, and a dietician [68,69]. There are different models of multidisciplinary teams: inpatient facility, community rehabilitation facility, and synchronized multidisciplinary treatment in the community.

However, despite this understanding, national and international surveys constantly identify problems with service implementation [70–72]. One way to tackle this is to provide good evidence to payers and service providers that the approach provides opportunities for efficiencies. From the nursing perspective, there is ample evidence that Parkinson's nurses, improve patients sense of well-being, save money and improve care [73,74]. Parkinson's nurses can provide a range invaluable services, from nurse prescribing, to support of infusion therapies (levodopa and apomorphine), timely referral to other services, not to mention patient and caregiver education and emotional support [69]. From the perspective of the allied therapy services, one of the main barriers has been to demonstrate consistent efficacy and cost benefits [75]. While most physiotherapy trials have shown short-term benefits, most of the observed differences between treatments have been small and the studies have not been of high quality [76]. Nevertheless, systematic reviews have found that physiotherapy interventions such as balance training combined with muscle strengthening, range of movement and walking training exercise, are effective in improving balance in patients with Parkinson's disease and more effective than balance exercises alone [77]. Complementary physical therapies such as dancing, hydrotherapy and robotic gait training also appear to be of therapeutic benefit, increasing mobility and quality of life in some people living with PD [78].

In terms of randomized controlled trials, the evidence base is relatively small. Sturkenboom et al. conducted a randomized controlled trial to evaluate the efficacy of occupational therapy for PD. In this study, home-based, individualized occupational therapy led to an improvement in self-perceived performance in daily activities in PD patients vs. control therapy [79]. More recently, Monticone et al. reported a randomized controlled trial that demonstrated a 25-point difference in MDS-UPDRS scores as well as quality of life in favor of inpatient multidisciplinary rehabilitation versus nursing care plus 'standard' physiotherapy (both groups received the same duration of PT intervention) [80]. The question remains which types of physical and occupational therapies provide the most benefit, and how the cost of these interventions balance against the costs of hospitalization and institutionalization. This area of research deserves urgent attention.

3.5. Nursing home and end of life/palliative

In the final stages of PD, it is now vital to consider that our patients are now living longer with their disease and co-morbidities. A growing body of evidence highlights a high burden of difficult-to-manage and highly debilitating non-motor symptoms (e.g. constipation, loss of bladder control, swallowing difficulties, drooling, breathlessness, sleep problems and pain) [81,82], significant caregiver distress [83,84], and a high utilization of medical services especially in the last year of life [85]. At this stage, many patients move into nursing homes for their care, where the majority of patients require support in performing activities of daily living [86]. However, neurologists and PD nurses often lose track of these patients and continuity of medical care can be difficult for these patients to access. In the US, one study of large Medicare patients found that only a third (33%) of nursing home residents with PD had outpatient neurologist care [85]. In a qualitative study conducted in the Netherlands, patients reported a similar lack of access, as well as a lack of emotional support and insufficient staff knowledge on PD-related issues (e.g. motor fluctuations and the need for adherence to medication timing) [87].

The lack of understanding of PD-related issues is also of key concern when considering perioperative periods. People with advanced PD often have a wide range of comorbidities and surgery (particularly urological, ophthalmological and orthopedic procedures) is common. Retrospective database studies have shown that compared with age-matched controls, PD patients undergoing surgery have longer hospital stays, more perioperative complications and higher in-hospital mortality [88–90]. This is because, when hospitalized, patients with PD face some unique challenges related to medication management, mental status changes, infections, and emergence of psychiatric symptoms, and there is a lack of awareness of simple solutions such as parenteral administration of dopaminergic medication during long surgeries [91]. It is therefore very important to recognize problems that may arise upon hospitalization of a patient with PD and provide education to health care professionals involved in the inpatient care of patients with PD.

In the very end stages, the complexity of patient needs may require specialist palliative care involvement that aims to deliver physical, psychological, emotional and spiritual care for patients and their caregivers. However, current medical systems have yet to adequately respond to this need through the provision of palliative care services to both PD patients and to affected families [92, 93]. For example, most people prefer to receive end-of-life care in familiar surroundings rather than in hospital, and hospitals are rarely set up to provide such services. Nevertheless, an international survey of 11 countries found that a substantial proportion (up to 75% in some countries) of PD deaths occurred in the hospital setting [94]. A key barrier to the development of palliative care pathways is the lack of evidence-based knowledge on how to build a service that integrates neurological and palliative care [95, 96]. Uncertainty about the timing of palliative care means that often it is not considered until a patient reaches crisis point, despite the recognized need for early planning due to increased prevalence of dementia [97]. More work also is needed to prevent inappropriate hospital transfers near death – for example by providing training and education regarding the needs of people living with very advanced PD.

4. Summary and conclusions

In recent years, there has been tremendous progress in our understanding of the underlying pathology of PD, together with an increasing recognition that PD is more than a motor disorder caused by dopamine degeneration. However, as might be expected, there has been a time lag in drug development with few novel therapies coming to market in recent years [98, 99]. For PD research to move forward, we need to consider the impact of the numerous recent insights on the development of new drugs and tailored strategies. For many years, our focus has been on developing new oral medications, but it is increasingly apparent that problems with the GI system appear early in PD and can affect how oral medications are absorbed. This supports the recent surge in interest in

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non-oral therapies which bypass the GI system.

It also is timely to consider the projected increases in PD prevalence. Service provision plans for our aging population should consider how a multidisciplinary team can increase efficiencies, and treatment plans should consider the full patient journey – from early diagnosis through to end of life care.

Conflict of interest

KRC, RB and TvL report fees for consultancy from Britannia Pharmaceuticals.

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